Module 3: Cancer Biomarkers and Tumor Profiling

1. The role of biomarkers in the oncology pipeline

Biomarkers are measurable indicators integrated throughout the oncology pipeline to guide clinical decision-making from screening to surveillance.

In screening and early detection, serum PSA enables prostate cancer identification in asymptomatic men, while CA-125 combined with HE4 improves ovarian cancer specificity. **Differential diagnosis** employs tissue biomarkers like EGFR mutations to distinguish adenocarcinoma from squamous lung carcinoma, avoiding misclassification.

For prognosis, multigene panels such as Oncotype DX predict breast cancer recurrence risk, informing adjuvant therapy decisions.

Predictive biomarkers stratify treatment response HER2 amplification identifies trastuzumab-eligible patients, while PD-L1 CPS ≥10 selects immunotherapy responders.

Finally, **monitoring** uses serial CEA for colorectal cancer response assessment and ctDNA for minimal residual disease detection post-therapy.

This structured framework, validated through Pepe's five-phase development model, ensures biomarkers transition from discovery to clinical utility with established analytical and clinical validity.

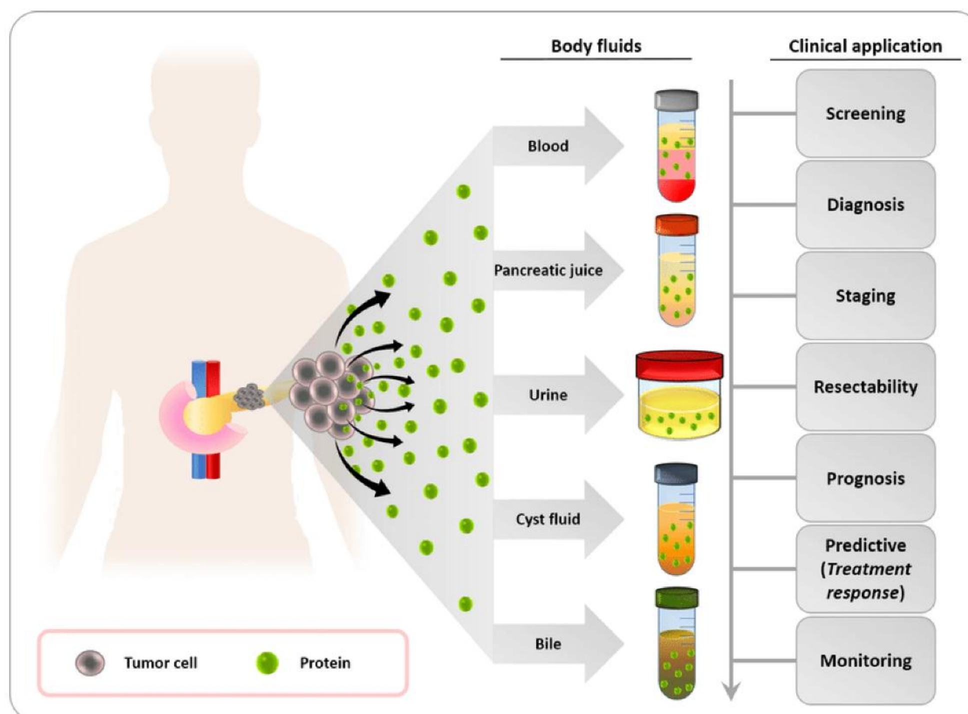

Figure 1.Identification of possible protein biomarkers for pancreatic cancer using bodily fluids (https://www.mdpi.com/1424-8220/24/1/37)

2. The ctDNA paradox: High hopes vs. Reality

Circulating tumor DNA (ctDNA) promised noninvasive, real-time cancer monitoring, but clinical translation reveals significant limitations that temper early enthusiasm (https://pmc.ncbi.nlm.nih.gov/articles/PMC9197509/)

Universal screening: Expected pan-cancer early detection but shows low sensitivity (<50%) for early-stage/low-shedding cancers like pancreas and glioma, requiring >90% variant allele frequency (VAF) for reliable detection.

MRD detection: Anticipated ultrasensitive minimal residual disease tracking demonstrates 30-40% discordance with tissue biopsy and frequent false negatives that miss low-burden disease.

Therapy monitoring: Projected immediate response assessment, however, suffers lead-time bias where ctDNA clearance lags radiological response by weeks, confounding treatment decisions.

Pan-cancer utility: Hoped-for universal applicability but achieves >95% sensitivity only in high-shedding tumors (lung, CRC) while performing <30% in others.

(https://pmc.ncbi.nlm.nih.gov/articles/PMC9197509/)

The complexity of ultra-deep sequencing for ctDNA makes it significantly more expensive than traditional protein-based markers, yet it often faces the same hurdles of low sensitivity for early-stage diagnosis.

3. The "Stagnation" of new biomarker discovery

No new FDA approvals: Since PSA (1986) and CA-125 (1990s), zero major novel cancer biomarkers have achieved guideline-recommended status for screening or diagnosis. HER2, BRAF V600E, and PD-L1 remain therapeutic predictors, not primary detection tools.

Clinical application	Biomarkers	Status
Investigation of pelvic mass	• CA 125 and HE4 (+ ROMA)[a]	• FDA-approved (2011)
	• CA 125 and 7 proteomic markers (+ Danish-Index)[b]	• FDA-approved (2009)
Improve PSA specificity in screening	• Serum PSA and urine PCA-3 and TMPRSS2-ERG fusions[c]	• Pending FDA approval
Separate indolent from aggressive prostate cancer	• PTEN loss[c]	• More research necessary[e]
	• TMPRSS2-ERG fusions[3]	
Assess risk of malignancy of thyroid nodules with indeterminate results on biopsy	• HBME-1, Galectin-3 and CK19[d]	• More research necessary
Assess risk of malignancy of CT (± PET) imaging-identified indeterminate lung masses	• CEA, CYFRA 21-1, SCC, CA15.3, Pro-GRP, NSE	• More research necessary

Figure 2. Niche applications of combinations of biomarkers with Food and Drug Administration approval or with potential in the future (https://pmc.ncbi.nlm.nih.gov/articles/PMC3425158/)

False discovery crisis: High-throughput platforms generate thousands of "hits," but >95% fail external validation:

- **Pre-analytical artifacts:** Freeze-thaw cycles, hemolysis, collection tube type destroy protein epitopes

- **Cohort bias:** Discovery sets lack healthy controls; validation cohorts differ demographically
- **Statistical overfitting:** 1000-plex panels fit noise, collapse on independent testing

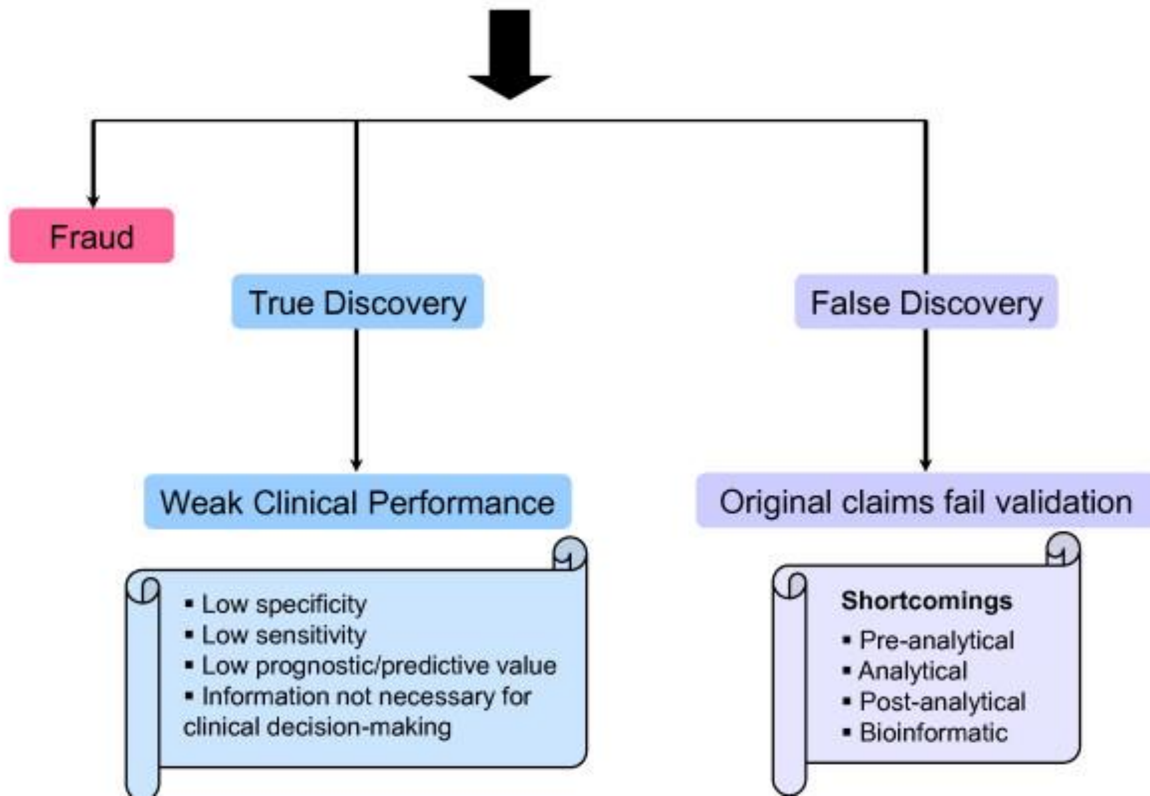

Figure 3.Summary of reasons for biomarker failure to reach the clinic (https://pmc.ncbi.nlm.nih.gov/articles/PMC3425158/)